Sepsis and the Clinical Laboratory

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DOI: 10.15428/CCTC.2013.211383
Sepsis Background and Significance

- Per year sepsis affects >750,000 American and >1.8 million patients worldwide per year.
- >200,000 septic patients die in the US/year.
- US hospital costs for sepsis are >$17 billion, with an uptrend of ~12%/year
- Severe forms of sepsis require ICU care – sepsis prevalence in medical ICUs is >40%
- Leading cause of death in non-cardiac ICUs
Pathophysiology of Sepsis

Systemic Inflammatory Response → Coagulation Activation → Impaired Fibrinolysis → End organ dysfunction → Hypotension
“Gold Standard” Diagnosis of Sepsis = SIRS + Infection

SIRS

- Temp > 38 or < 36°C
- WBC > 12 or < 4 x 10^3 cells/uL (x10⁹ cells/L)
- HR > 90 beats/min
- RR > 20 breaths/min

Infection

Pathogen identified in Culture of:
- Blood
- Urine
- Other
- Viral
- Fungal
- Parasitic
- Bacterial
- Other
- Burns
- Trauma
- Pancreatitis
- Other

Mortality Depends on Severity

- **Septic Shock**
  - Severe Sepsis + Hypotension
  - 40 – 70% Mortality

- **Severe Sepsis**
  - Sepsis + Organ Dysfunction
  - 25 – 30% Mortality

- **Sepsis**
  - SIRS + Infection
  - 15 – 20% Mortality

Early antimicrobial therapy is critical for survival in septic shock

Rapid initiation of treatment reduces mortality

Evolving Sepsis Definitions and Biomarkers

"life-threatening organ dysfunction caused by a dysregulated host response to infection"
Sepsis is a “life-threatening organ dysfunction caused by a dysregulated host response to infection”

Sepsis clinical parameters:
- Documented or suspected infection
- SOFA score >2

Septic Shock is “a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with greater risk of mortality than sepsis alone”

Septic Shock Clinical Parameters:
- Requirement for vasopressors to maintain art pressure >65 mm Hg
- Serum lactate > 2 mmol/L (with no hypovolemia)
- ED and outpatient quickSOFA (qSOFA) ≥ 2: Resp Rate ≥22/min, Altered mental status or Systolic Blood pressure ≤ 100 mm Hg

Definition adapted from: Singer M, et
Lactate in Sepsis Management

• End-product of anaerobic glycolysis and is Increased with:
  • Excessive energy demands - Tissue hypoperfusion (shock)
  • Low oxygen supply - Impaired cell metabolism
  • Impaired gluconeogenesis

• Not a useful marker for diagnosis of early disease

• The Surviving Sepsis Campaign advocates measuring lactate within 6 hours of presentation
  • Guide resuscitation to normalize lactate

• Elevated Lactate > 4 mmol/L is associated with in-hospital mortality

• Lactate Clearance can predict response to therapies and mortality
  • Goal Clearance >10% in first 6 hours
Procalcitonin an Ideal Sepsis Biomarker?

- Precursor to **Calcitonin**-expressed by thyroidal C-cells in healthy patients
- **Inflammation**—Synthesis is upregulated by cytokines in non-thyroidal cells with no cleavage of pro-sequence
- **Sepsis**—Concentrations correlate with disease severity and response to therapy
Utility of PCT in Sepsis

• **Diagnosis of Early Sepsis**
  – Prediction of infection in SIRS patients – Sens/Spec = 70%

• **Prediction of Prognosis**
  – Decreasing/low PCT – reduced mortality compared to increasing PCT

• **PCT to Monitor Therapy**
  – Evidence based guidelines don’t agree
  – Decreasing trend in in adults may be used along with other laboratory and clinical symptoms to direct antibiotic cessation
  – Less is known about pediatric patients
  – No utility in preventing the number of “superbugs”
Diagnostic Utility of CRP in Sepsis

- Acute phase reactant synthesized in the liver
- Up-regulated in response to inflammation
- Not as good as PCT at predicting early sepsis
- Can be used to Predict Prognosis in patients on antimicrobial therapy
- Cannot be used to Guide Antibiotic Therapy
Diagnostic Utility of Inflammatory Markers to Predict Sepsis

➢ Cytokines
   – Rapidly upregulated after infectious insult
   – Alone - diagnostic utility similar to PCT
   – Panel – superior diagnostic strength to identify sepsis

➢ Prediction of Prognosis
   – IL-6 excellent predictor of mortality

➢ Therapy Guidance
   – more studies needed

Adapted from: Meisner M. Clin Chem Acta 2002;323:17-29
Sepsis Biomarker – Score Card
Which Biomarkers and When?

“Gold Standard” – Bacterial, Viral, or Fungal Cultures - Slow, unreliable, and not always indicated (i.e. patients on antimicrobials)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sepsis vs SIRS</th>
<th>Prognosis</th>
<th>Therapy</th>
<th>Standard of Care</th>
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<td>Lactate</td>
<td>No</td>
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<td>Yes</td>
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<td>Procalcitonin</td>
<td>No</td>
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<td>CRP</td>
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<td>Multimarker</td>
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Conclusions

• Sepsis is a complex disorder associated with significant morbidity and mortality
• Diagnosis of sepsis in early stages is difficult because clinical signs and symptoms and lab tests are not sufficiently sensitive or specific.
• The clinical utility of current sepsis biomarkers is for prediction of disease severity, prognosis and monitoring therapy
• A better understanding of the pathobiology of early sepsis may facilitate identification of better diagnostic markers
References


Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: None declared
- **Consultant or Advisory Role**: None declared
- **Stock Ownership**: None declared
- **Honoraria**: Radiometer, Sysmex
- **Research Funding**: Siemens Healthcare Diagnostics, Sysmex
- **Expert Testimony**: None declared
- **Patents**: 61/757,393
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